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Neutropenias Following Allogeneic Bone Marrow Transplantation: Response to Therapy With High-Dose Intravenous Immunoglobulin

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Cytopenias following bone marrow transplantation may be severe and life-threatening. These have been described post-allogeneic Klumpp, 1991: *Bone Marrow Transplant* 8:159–171. or post-autologous bone marrow transplants Khouri et al., 1994: *J Clin Oncol* 12:748–758. as well as with peripheral blood stem cell transplantation Klumpp et al., 1992: *Am J Hematol* 41:215–217. It can be immune mediated, associated on occasions with graft-versus-host disease (GVHD) Anasetti et al., 1989: *Blood* 4:1054–1058; however, in most cases, the underlying mechanism is uncertain. The treatment of post-transplant cytopenias is not well established, and they are often refractory to immunosuppressive therapy with steroids. Herein we describe two cases of neutropenia after allogeneic bone marrow transplantation that improved after therapy with high-dose intravenous immunoglobulin. © 1996 Wiley-Liss, Inc.

Key words: neutropenias, post ABMT and IVIG

CASE REPORT 1

A 47-year-old man with chronic lymphocytic leukemia was treated upon diagnosis at another institution, with chlorambucil, prednisone, and Campath-IH monoclonal antibody (mAb). Upon relapse of his disease, he was refractory to treatment with CHOP, and later to fludarabine. He received a matched unrelated bone marrow transplantation for a stage Rai IV, Binet C disease. The preparative regimen consisted of cyclophosphamide 60 mg/kg/day bid and fractionated total body irradiation of 1,200 cGy given in four daily fractions. A combination of FK-506 and methotrexate was used for prophylaxis against GVHD, as per institutional protocols. Pretransplant, his leukocyte count was 73.2×10^9/L, consisting mostly of abnormal lymphocytes; the platelet count was 27×10^9/L, and the hematocrit 0.253.

The hospital course was complicated by fever of unknown origin that started on day 7 post-transplantation. Vancomycin and ceftazidine antibiotic therapy were started. Blood and urine cultures as well as a chest radiograph were normal. Amphotericin B was added on day 13. Because of recurrent fever on day 17, ceftazidine was changed to imipenem and doxycycline.

High-dose fluconazole was started because of prior history of cryptococcal meningitis 2 years ago; the current serum cryptococcal level was 1:16. A lumbar puncture was not possible because of persistent thrombocytopenia that was refractory to platelet transfusions. After an initial response, the patient had recurrent fever; on day 24, imipenem and doxycycline were changed to ticarcillin–clavulanate.

The patient's lymphocytosis persisted until day 13 of his transplant. His maximum neutrophil count was 0.3×10^9/L. This did not improve with high doses of granulocyte colony-stimulating factor. Vancomycin, fluconazole,

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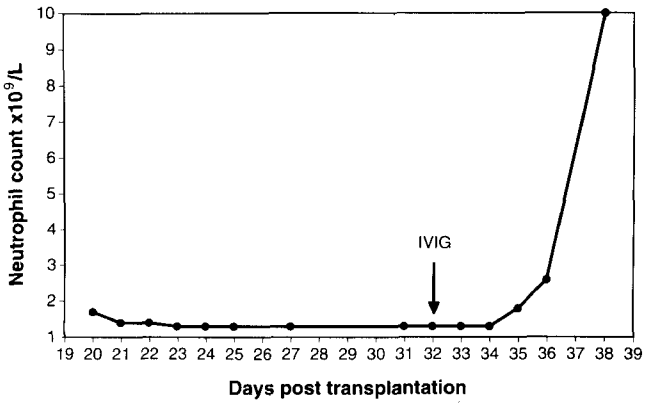

Fig. 1. Neutrophil count after bone marrow transplantation. Before and after treatment with intravenous immunoglobulin (IVIG).

and acyclovir were discontinued on day 28 with consideration of possible bone marrow suppression. Bone marrow aspiration and biopsy were obtained on day 26 and showed a cellularity of 45–50% with about 40% involvement of the cellular elements by chronic lymphocytic leukemia. Flow cytometry showed that 67% of the lymphocytes were clonal B cells. Restriction fragment length polymorphism showed mixed chimerism. Bacterial, fungal, and viral cultures of the bone marrow were negative.

Intravenous immunoglobulin at a dose of 400 mg/kg/day was administered daily for 5 days starting on day 32. At that time the leukocyte count was 0.3 $\times$ 10^9/L with a neutrophil count of 0.1 $\times$ 10^9/L, increasing to 2.0 and 1.2 $\times$ 10^9/L, respectively, on day 36. Three days later, the leukocyte count was 10 $\times$ 10^9/L (Fig. 1). At the same time, the patient has become platelet transfusion independent. His recovery persisted after discontinuation of the intravenous immunoglobulin and he is currently alive and in remission at 100 days post-transplant. The current neutrophil and platelet count is 6.5 $\times$ 10^9/L and 75 $\times$ 10^9/L, respectively.

CASE REPORT 2

A 32-year-old man received a one antigen-mismatched bone marrow transplant for chronic myelogenous leukemia in second chronic phase following a lymphoid blast crisis. He received a T-cell-depleted marrow graft, in addition to cyclosporine/methotrexate for prophylaxis against GVHD. His treatment was complicated by grade 2 GVHD of the skin on day 23, which responded to methylprednisolone therapy (2 mg/kg/day). This has recurred, however, with stage 2 cutaneous GVHD on day 83. Subsequently, he developed chronic GVHD of the skin. This was treated with cyclosporine and methylprednisolone. Later, the cyclosporine was discontinued because of renal insufficiency.

At 6 months post-transplant, the patient was admitted to the hospital with fever and sinusitis. He was pancytopenic and refractory to platelet transfusion. A bone marrow analysis showed a cellularity of 15% with no evidence of leukemia. Megakaryocytes were decreased. He recovered from his infection with vancomycin and ceftazidine antibiotic therapy and was discharged from the hospital. The leukocyte count, however, never achieved a level beyond 2.0 $\times$ 10^9/L despite daily use of granulocyte colony-stimulating factor treatment. One month later, he was readmitted to the hospital with right-sided chest pain and hemoptysis. A chest radiograph showed a right lung infiltrate suspicious of fungal etiology. His neutrophil count was 1.4 $\times$ 10^9/L, platelet count of 17 $\times$ 10^9/L. Direct platelet antibody testing was positive. He was started on intravenous immunoglobulin of 400 mg/kg/day. This resulted in an increase of the neutrophil count to 6.6 $\times$ 10^9/L within 2 days and the platelet count to 46 $\times$ 10^9/L, independent of transfusions, after a 5-days course of therapy. The patient went on to recover fully from the pneumonia.

DISCUSSION

Cytopenias are an important cause of morbidity and mortality following allogeneic or autologous hematopoietic transplantation [5]. The underlying mechanism varies. In our report there is absence of neutrophils in the peripheral blood in the face of a cellular marrow with increasing myeloid activity, failure to respond to a trial of discontinuation of potentially offending drugs in the first patient, and the presence of platelet antibodies in the second one. This is suggestive of a possible immune etiology.

Antineutrophil antibodies (ANA) have not been evaluated in our report; however the underlying pathophysiology in immune-mediated cytopenias does not necessarily correlate with the presence of antiplatelet antibodies or ANA [6]. In almost all cases described in the literature, onset is usually delayed several months post-transplant. In our first case, however, there was a failure to recover the neutrophils and platelets after allogeneic transplantation. This could be related to the underlying disease, chronic lymphocytic leukemia, where on occasions autoantibodies can be produced even in patients with no evidence of disease secodnary to T-lymphocyte imbalance [2,7]. This could be caused by chemotherapy and radiotherapy cytotoxicity, producing thymic dysfunction with associated abnormality of suppressor T cells.

Intravenous immunoglobulin has been used successfully in some in patients with neutropenia unrelated to transplantation [8]. Responses have generally been of short duration. To my knowledge, this is the first reported case of failure of engraftment in chronic lymphocytic leukemia and in a patient with neutropenia associated GVHD who responded to therapy with intravenous immu-

noglobulin. The precise mechanism of this response is unclear. The explanations that have been put forward include reticuloendothelial blockade [9] and the possible antiidiotype suppression of antibodies [10]. The dramatic improvement coincident with the administration of immunoglobulin strongly suggests, but does not prove, a cause–effect relationship. The potential importance of this observation in preventing potentially fatal complications warrants further study to confirm the efficacy of intravenous immunoglobulin in post-transplant cytopenias and to determine its mechanism of action.

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